Author’s response to reviews

Title: Transcatheter arterial chemoembolization plus sorafenib versus transcatheter arterial chemoembolization alone to treat advanced hepatocellular carcinoma: A meta-analysis

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Author’s response to reviews:

Reviewer 1:

Comments to the Author

1. The authors should provide more information about the inclusion criteria. Which TACE protocol was be used. Were there any differences in between the included studies for both mono- and combination therapies. Same for sorafenib. Dosage and duration of treatment should be provided for each study. Why including patients which refused surgical treatment? They might represent a better prognosis?
The combination of TACE and sorafenib was used in a simultaneous or sequential setting?

Response 1: Thanks for your suggestion and advices. In the revised manuscript, we have provided more detailed information about TACE and sorafenib treatment options. In the included studies, there is no difference in age, sex and clinical stages between the mono- and combination therapies. In each study, dosage and duration of treatment has been provided. All the patients we selected were advanced hepatocellular carcinoma (HCC), who had lost the chance of surgery and their long-term prognosis are poor.

In addition, the combination treatment of TACE and sorafenib was used in a simultaneous setting. In combination group, sorafenib was given at 400mg twice daily within 3-7 days after TACE, until the disease progresses or patient dies.

2. Almost all studies included in the meta-analysis were performed in Asia. This should be addressed in the discussion.

Response 2: Thanks for your advice. In the revised manuscript, we have added some new data of patients from other countries, such as America, Japan and South Korea. However, most of the data were from Asia-Pacific region even after another two studies were added, and we have addressed this in the revised manuscript.

3. I miss some studies, however, which should be discussed or included or addressed why not included: e.g. SPACE-Trial, Lencioni et al. 2016; Kudo et al. 2011.

Response 3: Thanks for your suggestion. We re-examined the manuscript and agreed that it would be more persuasive to include the two studies which you have mentioned. Therefore, we have included these two studies in the modified manuscript. During this revision, we have re-calculated the data information, which was different from the previous one and has been detailed in the figures and tables. And, the final meta-analysis results still showed that the ORR, DCR and OS in the combination group were more effective than those in TACE treatment alone.

Reviewer 2:

Comments to the Author

1. The authors indicated that the results after the combination of sorafenib with TACE for patients with advanced HCC are disputable. But I don't know any disputable questions in the article. Please give us some related reports to introduce this situation in the part of Introduction or Discussion.
Response 1: We feel sorry for the unsuitable expression and add the related explanation in discussion section as following: ‘In recent years, many studies have shown the benefit from combination of TACE plus sorafenib for advanced HCC, but a few studies have raised questions. For instance, a meta-analysis published in Hepatology International in 2016 showed that the combination therapy did not improve OS (HR = 0.79, p = 0.235) in advanced HCC patients (Hepatology international 2016, 10(3):501-510.). Similarly, a SPACE trial published in Journal of Hepatology in 2016 also showed that the combination treatment did not improve OS (HR 0.898, p = 0.29) (J Hepatol 2016, 64(5):1090-1098.). Our study confirmed the combination treatment was a practicable measure for HCC patients by evaluating ORR, DCR and OS’. So the paper concluded that TACE plus sorafenib was superior to TACE treatment alone.

2. Why were all 12 studies collected in this study from Chinese? Are there not the similar data from the other countries?

Response 2: Thanks for your advice and we realized that the data seemed not convincing enough. So we made minor changes in our revised meta-analysis. We added 2 studies which included 765 patients from Europe, Japan and South korea, except original 12 studies which included 905 patients from China. Although the research data has been increased, the final conclusion has not been changed.

3. In addition, the explanation for the limitation in the Discussion is not very suitable.

Response 3: Thanks for your suggestion and we have made appropriate changes in discussion section as following: ‘However, there were some limitations to our study. First, the follow-up time was not sufficient. Second, the data we analysed are extracted from published papers rather than the original patient records, which can lead to bias in the analysis results and influence the accuracy of our conclusion. Third, this study demonstrated that 0.5-year OS and one-year OS can be extended, but a longer survival time has not been provided’.